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Norepinephrine clearance, chromogranin A and dopamine β hydroxylase in renal failure

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Norepinephrine clearance, chromogranin A and dopamine β hydroxylase in renal failure. Plasma norepinephrine (NE) levels are normal or elevated in patients with renal failure even though uremia often damages the sympathetic nerves that release NE. We infused ^{3}H-NE into subjects with normal, mildly depressed, or absent renal function. ^{3}H-NE clearance was depressed 20% in mild renal failure and 40% in patients on hemodialysis. The calculated rate of NE release into plasma was low in uremics even though their plasma NE was normal. Dopamine β hydroxylase (DβH) and chromogranin A are released from sympathetic nerve endings along with NE. DβH levels were low in uremia and DβH levels doubled following hemodialysis. Chromogranin A levels were very high in uremics and increased slightly following hemodialysis. Plasma clearance of both NE and chromogranin A appears low in renal failure. The calculated rate of NE release is diminished in uremics, which is in accord with reports of autonomic neuropathy in these patients.

Measures of sympathetic nervous function in renal failure patients present a curious anomaly. While clinical measures reveal impaired sympathetic nervous function, biochemical assays show normal or high blood levels of the sympathetic neurotransmitter norepinephrine (NE). This contrasts with other diseases associated with autonomic neuropathy, where NE levels are low [1–4]. Numerous studies have documented defective sympathetic nervous tone in patients with renal failure [5–9]. Failure of the sympathetic nervous system is thought to be an important component of hemodynamic instability during hemodialysis [10].

Fifty percent of patients on dialysis had autonomic dysfunction in one study [11]. Only one study reports low basal NE levels in hemodialysis patients [12] while several studies report slightly, but not significantly, elevated levels [13–16], and even more studies report significantly elevated plasma NE levels in patients on hemodialysis [17–26].

When the sympathetic nervous system is activated it exocytotically releases NE, dopamine β hydroxylase (DβH) and chromogranin A from nerve vesicles. Chromogranin A is the major component of these vesicles but has not been very thoroughly studied in renal failure. The levels of DβH are low in patients with end-stage renal failure [16, 19, 20]. This apparent contradiction of autonomic neuropathy, low plasma DβH levels, and yet elevated plasma NE levels in hemodialysis patients has been difficult to reconcile.

Plasma NE is primarily cleared by re-uptake into autonomic nerves and uptake into vascular tissue. The clearance of NE into these tissues is very rapid and provides a plasma clearance more than 10 times the glomerular filtration rate of normal subjects [27, 28]. Defective uptake of NE might explain why plasma NE levels are high even though NE releasing nerves are neuropathic. We have measured NE, DβH, chromogranin A and plasma NE clearance in normal subjects, subjects with mild renal insufficiency and patients dependent on hemodialysis.

Methods

Subjects for the NE studies included 13 normal adults (42 ± 4 years, 8 males) with serum creatinines of 0.78 ± 0.05 mg/dl. Five chronic renal insufficiency (CRI) patients had only one functioning kidney and were selected to have about half of normal renal function. They were 46 ± 7 years old (2 male) and had serum creatinines of 1.46 ± 0.39 and had stable renal function with no active kidney disease. Five hemodialysis patients (36 ± 5 years, 4 male) underwent hemodialysis three times weekly and had negligible renal function. No patients were taking drugs, such as methyldopa or clonidine, known to alter NE release. Patients who were clinically edematous or volume depleted were excluded from the study. Dialysis patients were studied on a between dialysis day when they were most likely to be in fluid balance. Subjects ranged from 53 to 84 kg except for one obese male who weighed 111 kg. At physiologic pH, NE is soluble in water, but not fat. The ^{3}H-NE volume of distribution was unrelated to obesity in these subjects. Prior to the ^{3}H-NE infusion all subjects ate a standard breakfast of a piece of fruit, a bread roll with a pat of butter and a decaffeinated beverage.

Plasma NE levels were measured by the catechol-O-methyltransferase (COMT) based radioenzymatic technique of Ziegler, Woodson and Kennedy [29]. Since uremic plasma can sometimes have an inhibitory effect on the enzyme COMT, NE levels were individually standardized for each group. NE clearance and release rates were measured as previously described using ^{3}H-NE of greater than 98% radiochemical purity [27]. Subjects were kept recumbent and ^{3}H-NE was infused into an antecubital vein at 1.5 μCi per min for 10 minutes and then the infusion rate was decreased to 0.78 μCi per min for 110 minutes. Plateau levels of ^{3}H-NE were attained in one hour

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Table 1. Sitting and standing BP of normal, CRI and HD patients

	Normal	CRI	HD	
			Pre-dialysis	Post-dialysis
Sitting BP	108 ± 5 / 66 ± 3	114 ± 3 / 71 ± 13	166 ± 4[a] / 100 ± 3[a]	150 ± 15[a] / 86 ± 7[a]
Standing BP	107 ± 4 / 73 ± 4	101 ± 3 / 66 ± 5	164 ± 5[a] / 99 ± 1[a]	129 ± 13[b] / 82 ± 9[b]

Blood pressure data from patients evaluated in Figs. 1–3.
Abbreviations are: CRI, chronic renal insufficiency; HD, hemodialysis.
[a] $P < 0.05$ vs. normal by t-test
[b] $P < 0.05$ vs. predialysis by paired t-test

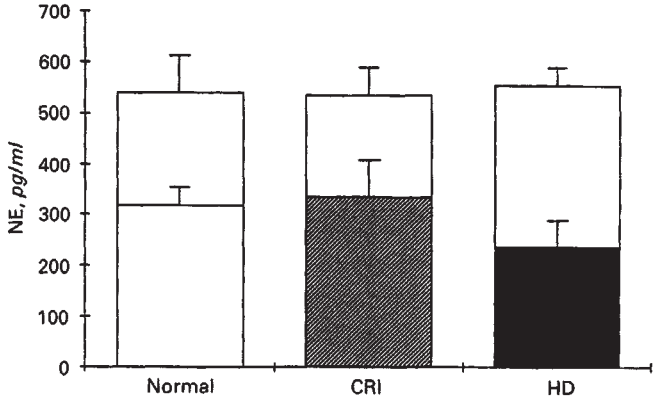

Fig. 1. *The lower bars show plasma NE levels while subjects were recumbent, and the upper bars show their NE levels after standing.* There were no statistically significant differences between groups. CRI = chronic renal insufficiency, HD = hemodialysis.

with this technique. Blood samples were drawn from the antecubital vein of the contralateral arm toward the end of the infusion to measure plasma NE and ^{3}H-NE levels and at preselected times after the infusion was abruptly terminated. The ^{3}H-NE content of the infusate and plasma samples was measured after alumina chromatography by scintillation spectroscopy. O-methylated metabolites of NE do not adhere to alumina. We checked for the presence of deaminated metabolites of NE by solvent extraction of plasma samples and found no measurable levels of ^{3}H-NE metabolites following alumina chromatography.

The rate of NE clearance from plasma was calculated by the formula:

$$\text{NE clearance liters per minute} = \frac{^3\text{H-NE infused per minute}}{^3\text{H-NE per liter plasma}}$$

NE release rate was calculated by the formula:

$$\text{NE release rate} = \text{NE clearance} \times \text{plasma NE concentration}$$

Bufano et al [30] have shown that d1 ^{3}H-NE and Linares et al [31] have shown that 1 - ^{3}H-NE kinetics follow a biexponential decay in human plasma which is approximated by the equation:

$$^3\text{H-NE} = (A \cdot e^{-\alpha t}) + (B \cdot e^{-\beta t})$$

where A and B are constants and α and β are the rate constants.

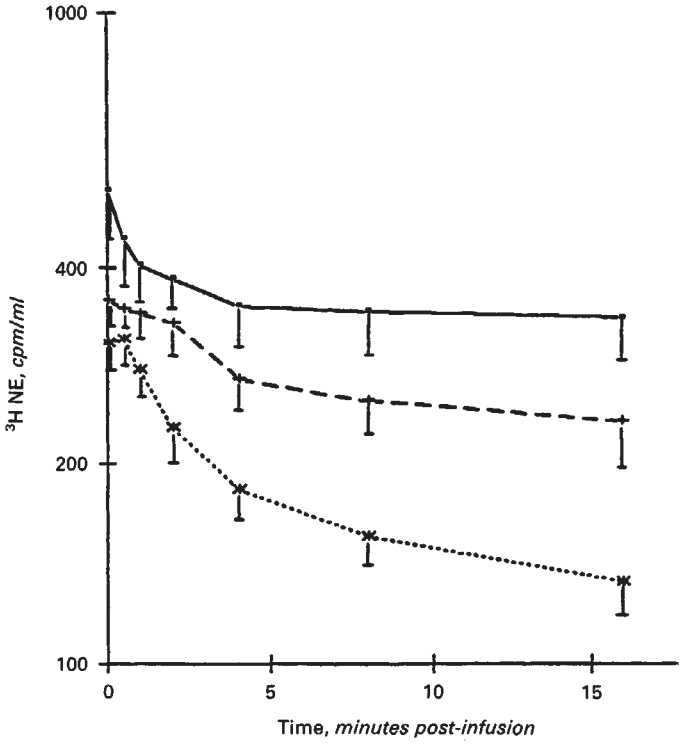

Fig. 2. *Plasma levels of ^{3}H-NE for 16 minutes after a two hour infusion of ^{3}H-NE was abruptly stopped.* Note log scale for ^{3}H-NE levels. Symbols are: (——) HD; (------) CRI, (.....) normal.

This equation describes the rate of decay of ^{3}H-NE in a two compartment model. The volume of distribution of the first compartment is then:

$$\text{Volume} = \frac{\text{clearance}}{\alpha}$$

and the half-life of ^{3}H-NE in the first compartment is:

$$t\tfrac{1}{2} = \frac{0.693}{\alpha}$$

The formula for the rate of decay of ^{3}H-NE was calculated by the program R-STRIP (Micro Math Scientific Software, Salt Lake City, Utah, USA).

Blood pressure was measured by auscultation in seated subjects and after they stood quietly for five minutes.

Plasma levels of DβH were measured in a second group of six control and nine uremic subjects, and chromogranin A levels were measured in a third group of nine control and 19 uremic subjects at a separate hospital. The hemodialysis patients had plasma levels measured immediately prior to the initiation of and immediately following hemodialysis. DβH activity was measured by the radioenzymatic assay of Molinoff, Weinshilboum and Axelrod [32] and chromogranin A levels were measured by a rapid modification [33] of the previously described radioimmunoassay of O'Connor et al [34, 35].

Data are expressed as the mean ± standard error of the mean. Statistical analysis is by one-way analysis of variance or Student's t-test.

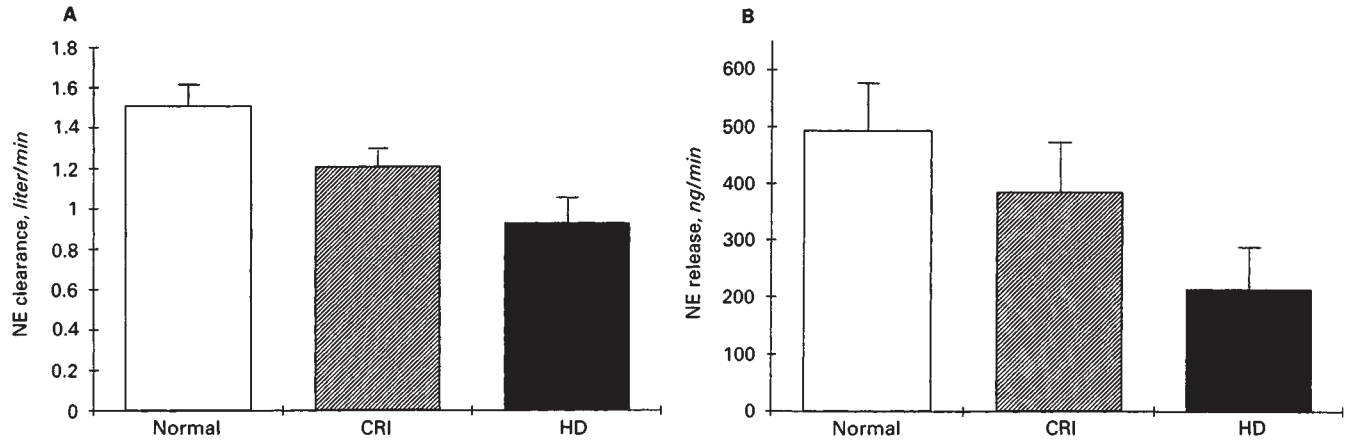

Fig. 3A. *NE clearance calculated from plateau levels of plasma ^{3}H-NE and the ^{3}H-NE infusion rate.* The groups differ significantly by ANOVA ($P < 0.004$). **B.** NE release rate calculated from NE clearance and basal plasma NE levels. The groups differ significantly by ANOVA ($P < 0.05$).

Table 2. Kinetics of ^{3}H-NE

	Normal	CRI	HD	*P*
Clearance *liter/min*	1.5 ± 0.1	1.2 ± 0.1	0.9 ± 0.1	0.003
A	187 ± 19	183 ± 58	179 ± 49	NS
α	0.4 ± 0.07	0.34 ± 0.03	1.23 ± 0.57	0.07
B	151 ± 7	192 ± 44	354 ± 47	0.001
β	0.0110 ± 0.003	0.0071 ± 0.004	0.0048 ± 0.0028	NS
t-½ short *min*	2.0 ± 0.3	2.1 ± 0.2	1.1 ± 0.4	0.112
Vd short *liter*	4.4 ± 0.8	3.8 ± 0.3	1.4 ± 0.4	0.066

A mathematical description of the decay curves in Fig. 2 when they are fitted to the biexponential equation:

$$^3\text{H-NE} = (A \cdot e^{-\alpha t}) + (B \cdot e^{-\beta t})$$

t-½ short is the half-life of the initial phase of the decay curve. Vd short is the volume of distribution of the initial phase of the decay curve. Abbreviations are: CRI, chronic renal insufficiency; HD, hemodialysis.

Results

The hemodialysis patients (HD) were mildly hypertensive prior to hemodialysis and had mild postural hypotension following hemodialysis (Table 1). Normal subjects, subjects with chronic renal insufficiency (CRI) and HD patients all had similar plasma NE levels while recumbent and standing (Fig. 1). ^{3}H-NE was infused into the normal subjects, CRI and HD patients to attain a plateau level of plasma ^{3}H-NE and then the infusion was abruptly discontinued. Plateau levels of ^{3}H-NE were highest in the HD group and next highest in the CRI group. ^{3}H-NE levels decayed in a biexponential fashion with no overlap between the three groups (Fig. 2). Since plasma ^{3}H-NE levels had reached steady state, NE clearance could be calculated from the infusion rate of ^{3}H-NE and plasma ^{3}H-NE levels. The clearance of NE in normal subjects was 1.5 liters per minute, higher than the clearance rate of 0.9 liters per minute in HD patients (Fig. 3A). The rate at which HD patients released NE into their plasma was less than half that of normal subjects (Fig. 3B). The HD patients had higher levels of plasma ^{3}H-NE at the end of the infusion (time point 0 of Fig. 2) so their clearance of ^{3}H-NE was less (Table 2). Nevertheless, their initial half-life for ^{3}H-NE is at least as short as that of normal subjects (Table 2), since the volume of plasma they clear may be smaller (Table 2). The late phase of the decay curve for ^{3}H-NE appears to be steeper for normal subjects than for HD subjects (Fig. 2), but assay variability was greatest at late time points because of low ^{3}H-NE counts.

Noradrenergic storage vesicles contain DβH and chromogranin A which are exocytotically released along with NE upon nerve stimulation. Plasma DβH levels were much lower in HD patients than in normal controls and doubled following hemodialysis (Fig. 4). In contrast, plasma chromogranin A levels were markedly higher in HD patients than in normal subjects and increased slightly with hemodialysis (Fig. 5).

Discussion

Patients with chronic renal insufficiency or complete renal failure had plasma NE levels that were not significantly different from those of normal subjects. This agrees with the findings of several other groups [13–16]. However, plasma NE levels are a poor guide to sympathetic nervous tone in patients with renal failure. The clearance of ^{3}H-NE from the circulation was significantly decreased in patients with renal failure. This finding disagrees with that of Schohn et al [18] who reported that plasma NE clearance was increased in renal failure. Their technique to determine NE clearance was markedly different from ours as they infused sufficient amounts of NE to raise blood pressure by 20 mm Hg and infused the NE for only 20 minutes, which may be insufficient time to obtain plateau levels. These different techniques may explain the disparate findings between Schohn [18] and this study since we have previously found indications that high NE levels stimulate NE clearance [36], that β-adrenergic agonists stimulate catecholamine clearance and that the enhanced clearance is blocked by propranolol [37]. In contrast, we infused ^{3}H-NE for two hours to attain plateau levels in plasma and infused a tracer amount that elevates plasma NE by less than 2%. The difference between our findings and those of Schohn et al [18] suggests that the defect in NE clearance of uremics may disappear under the influence of high plasma levels of NE, but we do not have an

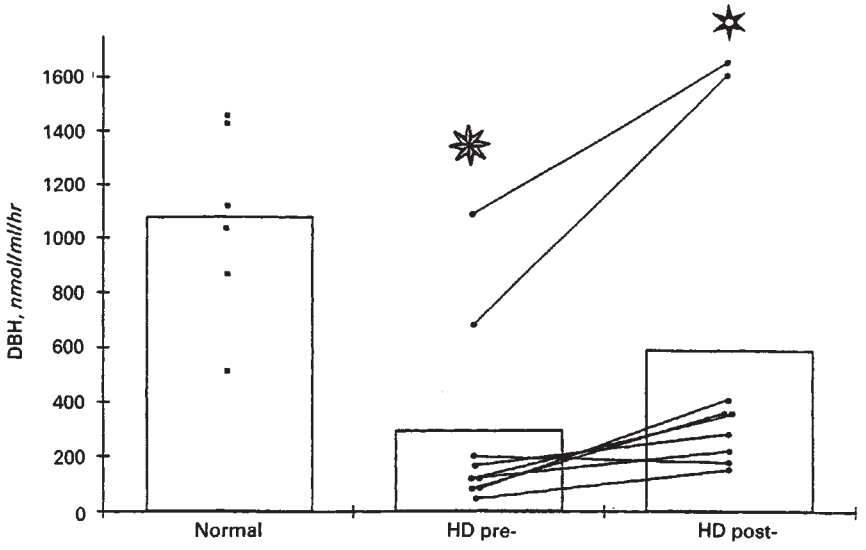

Fig. 4. *Plasma DβH activity in normal subjects, patients prior to hemodialysis (HD pre) and immediately following hemodialysis (HD post).* ✱ Different from normal by *t*-test $P < 0.001$. ✲ Significantly increased following hemodialysis by paired *t*-test $P < 0.01$.

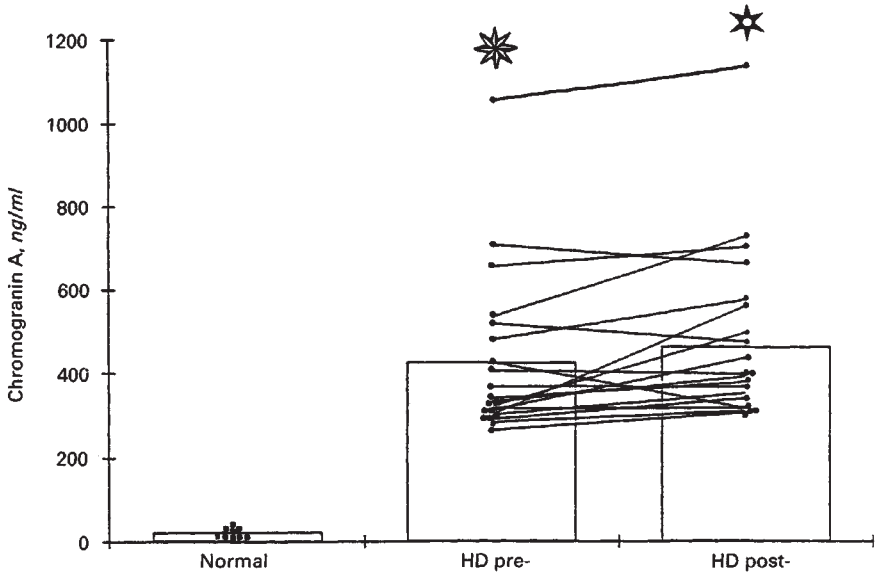

Fig. 5. *Plasma chromogranin A levels in normal subjects, patients prior to hemodialysis (HD pre) and immediately following hemodialysis (HD post).* ✱ Different from normal by *t*-test $P < 0.001$. ✲ Significantly increased following hemodialysis by paired *t*-test $P < 0.05$.

entirely convincing explanation for the differences between our findings and those of Schohn et al [18].

Table 2 presents a kinetic analysis of the NE decay curves based on a biexponential decay appropriate for a two compartment model of NE distribution. Linares et al [31] have used the CONSAM computer program to show that a two compartment model fits the decay curve of ^{3}H-NE better than other models tested. The CONSAM program gave similar, but not identical parameters when compared with the R-STRIP program on our data. The most reliable data obtained by this analysis is for NE clearance. Clearance is based on plateau levels of ^{3}H-NE, which can be measured repeatedly in the same subject. It is based on the highest (and thus most accurately measured) levels of ^{3}H-NE. In contrast, the values for B and β in Table 2 are based on the lowest ^{3}H-NE levels, subject to greatest variability.

When a drug is given acutely the initial half-life of a biexponential decay curve is often referred to as the distribution half-life. Under conditions of this experiment, however, the initial half-life does not represent distribution of ^{3}H-NE into a compartment that is not yet at plateau levels of ^{3}H-NE as ^{3}H-NE levels had plateaued for over an hour. The rapid decay phase is probably the result of rapid clearance of ^{3}H-NE from plasma by uptake-1 and uptake-2 mechanisms or transport into a compartment where ^{3}H-NE is rapidly cleared. Much of the removal of ^{3}H-NE from plasma appears to take place during the early phase in all three groups of subjects.

The patients with chronic, mild renal insufficiency had a ^{3}H-NE clearance intermediate between that of normal subjects and HD patients. In general, differences between ^{3}H-NE kinetics in normal subjects and those with mild chronic renal insufficiency attained only borderline statistical significance. The incremental change in ^{3}H-NE levels between normal subjects, chronic renal insufficiency patients and HD patients (Fig.

2) suggests a gradual decrease in NE clearance with decreasing renal function. It thus seems advisable to control for renal function in studies of NE and NE clearance. Defective NE clearance has been reported in old age [38] congestive heart failure [39] and essential hypertension [40–45]. These diseases are associated with impaired renal function, but studies of NE clearance in these diseases rarely report any measures of renal function.

Plasma NE levels overestimate the amount of sympathetic nervous activity in patients requiring hemodialysis. When plasma NE levels are corrected for this diminished clearance the calculated rate of NE release into plasma is significantly diminished in hemodialysis patients compared with normal subjects. These hemodialysis patients had a moderate decrease in blood pressure that characteristically follows dialysis (Table 1). None of them had the marked blood pressure variations characteristic of patients with severe autonomic neuropathy. This diminished NE release rate agrees with the many observations of autonomic insufficiency in uremics [5–9] and also agrees with our findings and other reports of low plasma DβH [16, 19, 20] in uremics.

Chromogranin A levels in patients requiring hemodialysis are higher than any estimates of increased sympathetic nervous activity in uremics. Chromogranin A is released from sympathetic nerves, the adrenal medulla and most other endocrine glands including the parathyroids. The mode of clearance of chromogranin A is unknown but plasma chromogranin A rises in direct parallel with the degree of renal insufficiency. Furthermore, when uremic plasma containing very high levels of chromogranin A immunoreactivity is size fractionated by gel filtration the immunoreactivity is found to reside in low molecular weight fragments of chromogranin A. These findings suggest that the kidney is a site of removal or disposition of chromogranin A or its immunoreactive fragments [33, 34].

There was a small increase in chromogranin A following hemodialysis that may partly be related to hemoconcentration (Fig. 5). However, DβH increased 92% after hemodialysis (Fig. 4). Both these molecules are far too large for effective clearance through hemodialysis membranes. There were large differences between DβH levels among both control subjects and those with renal failure (Fig. 4). The variability in DβH levels has a genetic basis [46] unrelated to renal failure.

NE is poorly cleared by patients requiring hemodialysis. Uncorrected plasma NE levels give an inaccurate estimate of sympathetic nervous activity in uremia. Impaired NE clearance in uremia cannot be completely explained by even a total lack of direct renal clearance or excretion. In a separate experiment we found that in eight subjects the clearance of ^{3}H-NE from plasma into urine was 0.17 liter/min while a simultaneous plasma clearance was 1.58 liter/min of ^{3}H-NE (full data to be published elsewhere). The clearance of ^{3}H-NE by normal subjects in this study of 1.5 liter/min exceeds predicted renal blood flow. NE is extracted from the bloodstream by most tissues [27, 31], and the impairment in NE clearance is more likely due to impaired tissue uptake of NE [28]. Impaired NE clearance has the practical consequence of requiring a correction factor when plasma NE levels are used as an index of autonomic function in uremics. The alteration in NE clearance may also have important effects on blood pressure. Tricyclic antidepressants impair uptake-1 mediated clearance of NE and cause postural hypotension. The glucocorticoids impair uptake-2 mediated NE clearance and cause hypertension. Uremics often develop both postural hypotension and recumbent hypertension.

In summary, all of the biochemical indices of sympathetic nervous function that we measured in uremics were abnormal except for plasma NE. The "normal" levels of plasma NE were the result of a slow rate of NE release and decreased NE clearance.

Acknowledgments

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